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Examining Authority for the Patent Cooperation Treaty

Applicants:	Drexel University
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By Susan M. Heritage
Susan M. Heritage

Assistant Commissioner of Patents
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Dear Sir:

RESPONSE TO WRITTEN OPINION

This is in response to the Written Opinion mailed 18 April 2001. Reconsideration of this application is respectfully requested.

Claim 8 has been acknowledged to have novelty.

Claims 1-7 and 9-14 have been suggested to lack novelty under PCT Article 33(2) as being anticipated by Rasor et al. The reference is suggested to teach a composition for ultrasound imaging comprising a microparticle having a hydrophobic surface and a gas microbubble attached or in contact with the microparticle. Applicants respectfully disagree.

Applicants' invention is a surface stabilized microbubble for use as an ultrasound contrast agent to enhance ultrasound detection of objects. The microbubbles

are made of microparticles having hydrophobic surface properties or affinity toward specific gases, and a gas microbubble which attaches to or encapsulates the microparticle.

Rasor et al. teach a composition for contrasting of the right heart and left heart. The microparticles of the composition are only lipophilic and are not taught to have any affinity for specific gases. Rasor et al. teach a mixture of (1) a fatty acid, (2) a non-surfactant solid and (3) an amount of gas effective to produce a suspension of microbubbles when the microparticles are dispersed in water. Rasor et al. also teach that a solid particulate microbubble precursor may be associated with a solid lipophilic group-containing compound effective to prevent the dissolution of an echogenic entity. Nowhere does Rasor et al. teach or suggest a gas microbubble attached to or encapsulating a microparticle. Further, Rasor et al. teach both a fatty acid and non-surfactant solid as essential components of the microparticle. It is not taught or suggested that the microparticles could be made up of less than both components. Accordingly, the present invention can not be held to lack novelty with regard to Rasor et al.

Applicants respectfully request reconsideration and withdrawal of the objection of claims 1-7 and 9-14 under PCT Article 33(2).

Claims 1-7 and 9-14 have also been suggested to lack novelty under PCT Article 33(2) as being anticipated by Schneider et al. The Examiner suggests that Schneider et al. disclose a composition for ultrasound imaging comprising a microparticle having a hydrophobic surface and microbubbles associated therewith. Applicants respectfully disagree.

Schneider et al. teach gas filled microbubble liposome suspensions usable for imaging contrast agents in ultrasonic echography. The introduction of gas into the liposome solution is effected by forcing gas into the liposome solution or agitating the solution to entrap gas. Schneider et al. do not teach or suggest a gas microbubble which attaches to or encapsulates the microparticle. The gas is simply dispersed within the solution. Accordingly, the present invention can not be held to lack novelty with regard to Schneider et al.

Applicants respectfully request reconsideration and withdrawal of the objection of claims 1-7 and 9-14 under PCT Article 33(2).

Claims 1-14 have been suggested to lack inventive step under PCT Article 33(3) as being obvious over Rasor et al. or Schneider et al. in view of Unger et al. It is suggested that Unger et al. disclose compositions comprising microbubbles which are useful for both ultrasound imaging and drug delivery. It is further suggested that it would have been obvious to one of skill in the art to use the compositions disclosed by Rasor et al. or Schneider et al. for drug delivery by insonating the microbubbles at a desired site *in vivo* because Unger et al. teach that gas-filled microbubbles may further contain drugs to yield a drug delivery means having the advantage of site-specific delivery. Applicants respectfully disagree.

Unger et al. teach a drug delivery compositions with temperature activated gaseous precursor filled microspheres comprising a therapeutic compound. The microspheres may be used for targeted therapeutic delivery *in vivo* or *in vitro*. The microsphere is relatively spherical in shape with an internal void. The therapeutic compounds are released when

the compound reaches a selected activation or transition temperature.

As set forth previously, neither Rasor et al. nor Schneider et al. teach surface stabilized microbubbles made of a microparticle having hydrophobic surface properties or affinity toward specific gases, *and* a gas microbubble which *attaches to or encapsulates* the microparticle. Similarly, Unger et al. fail to provide any teaching or suggestion of a microparticles having hydrophobic surface properties or affinity toward specific gases; or gas microbubbles which attaches to or encapsulate the microparticle. Accordingly, these references when combined fail to provide the requisite teaching to anticipate or render obvious any claims to the microbubble of the present invention.

Further, the drug delivery system of Unger et al. is temperature activated. There is no teaching or suggestion that this system would be effective with microbubbles which were not heat activated. Accordingly, it would not have been obvious for one skilled in the art to use a microbubble of Rasor et al. and/or Schneider et al. in the delivery system of Unger et al. Even if the microbubble of the recited prior art were to be utilized in the system of Unger et al., the present invention would still not be achieved, as none of the references teach or suggest a gas microbubble which attaches to or encapsulates the microparticle, or a method of delivering a drug to a selected site using a microbubble as taught by the present invention.

Thus Applicants respectfully request reconsideration and withdrawal of the objections of claims 1-14 under PCT Article 33(3).

Respectfully submitted,

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